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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,605	05/31/2002	Ulrike Fiedler	1406/37	8368

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EXAMINER	
LEE, MATTHEW C	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 02/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,605	FIEDLER ET AL.	
	Examiner	Art Unit	
	Matthew C Lee	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/22/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *17-25,29-41 and 43-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,26-28 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/13/02, 11/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I, claims 1-16, 26-28 and 42, drawn to protein with beta-sheet structure, classified in class 500, subclass 324.

Group II, claims 17-18 and 36-41, drawn to polynucleotide, vectors, host cells and method of expressing proteins using said vectors and host cells, classified in class 435, subclass 320.1.

Group III, claims 20-24 and 29-35, drawn to a method of preparing proteins with beta-sheet structures, classified 435, subclass 69.1.

Group IV, claim 25, drawn to a method of preparing a chemical composition, classified in class 435, subclass 69.1.

Group V. Claims 43-45, drawn to a method of preparing a gamma crystalline protein with a new binding property. classified 435, subclass 69.1.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The inventions listed as group I-V do not related to a single general inventive concept under PCT Rule 13.1 because under PCT 13.2, they lack the same or corresponding special feature for the following reasons:

The feature of Group I (claims 1-16, 26-28 and 42), protein with beta-sheet structure, is taught in the art (Devlin, Thomas M, Textbook of Biochemistry : With Clinical Correlations, 1999, p44) and therefore is not considered a special technical feature among the inventions of Groups I-V. As the claims do not recite a special technical feature, they are not joined by a general inventive concept and lack unity.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

Multiple species of crystalline protein: alpha-crystalline, beta-crystalline and gamma-crystalline, gamma-II-crystalline. (e.g. claims 8 and 9).

Multiple species of molecular property: an antigen binding specificity and a catalytic activity (e.g. claim 13).

Multiple species of crystalline protein from different vertebrate species: bovine, rodent, bird and fish (e.g. claim 26).

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

Regarding species of claim 8, 9 and 26:

Although chemical compounds of claim 8 and 26 (protein selected from different vertebrate species) share a common structure of beta-sheet, the compounds are not regarded as lacking a unified inventive concept because bovine crystalline is known in the art (Xia et al. Science, 1997, v277, p60-66).

Regarding species of claim 13:

The two measurements of claim 13 are not regarded as being of similar nature because they measure different aspects of a molecule's property, and are therefore not joined by a general inventive concept with regard to molecular property.

During a telephone conversation with Mr. Richard Jenkins on 1/18/2005 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-16, 26-28, and 42 as well as election of the species bovine gamma-crystalline, and antigen-binding specificity. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-25, 29-41 and 43-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, or species.

During the course of examination, it was determined that lipocalin does not pose an additional search burden, therefore, lipocalin is rejoined with the elected group and will be examined along with bovine gamma-crystalline as the two elected species.

An action on the merits of the claims of Group I, as they read on the elected species, follows:

Information Disclosure Statement

Information disclosure statements filed by applicant on August 13, 2002 and November 22, 2004 have been fully considered.

Amendments

Preliminary amendments to the specification and claims filed on January 9, 2002, and May 28, 2003 have been entered.

Claim Objections

All dependent claims are objected to for the following informality. The dependent claims should begin with "The protein of..." instead of "Protein according to..."

Claim Rejections – 35 U.S.C. 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the dependent clause "wherein amino acids exposed on a surface of at least two β-strands exposed on a surface of at least one beta sheet exposed on a surface of the protein" is confusing. The repeated use of "exposed" obfuscates the relationship among the objects referred to in the claim and it is not clear how the amino acids are related to the surface and beta sheet of the protein.

Regarding claim 3, the dependent clause "wherein amino acids exposed on the surface of three beta strands exposed on the surface of the protein" is also confusing for the same reason as set forth above.

Claim Rejections – 35 U.S.C. 102(a)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6, 10, 11, 13, 16, 27, and 28 are rejected under 35 U.S.C. 102(a) as being anticipated by Beste et al. (PNAS, March 1999, v96, p1898-1903).

Claim 1 is directed to a protein with beta-sheet structure wherein amino acids exposed on a surface are mutagenized for a new antigen binding specificity. **Claim 2** further limits the protein of claim 1 to be selected from the group consisting of a crystalline, a spheruline, a heat shock protein, a cold shock protein, a beta-helix protein, a lipocalin, a serpin, a fibronectin, a transcription factor, a GFP, a NGF, a tendamistat and a lysozyme. **Claim 3** further limits the mutagenized amino acids of claim 1 to be those exposed on the surface of three beta strands. **Claim 4** further limits the mutagenized amino acids of claim 1 to be those exposed on the surface of at least four beta-strands. **Claim 5** further limits the mutagenized amino acids of claim 1 to be those on the surface of at least two beat strands of at least two beta sheets. **Claim 6** further limits the mutagenized amino acids of claim 1 to be those exposed on the surface of three beta strands of two anti-parallel beta sheets. **Claim 10** further limits the mutagenized amino acids of claim 1 to be in a solvent accessible region. **Claim 11** further limits the mutagenized amino acids of claim 1 to be in a region selected from beta sheet of a domain or sub-domain. **Claim 13** further limits the protein of claim 1 to

comprise mutations in exposed surface amino acids that confer a new antigen binding specificity. **Claim 16** is directed to a composition comprising the protein of claim 1 and at least one other protein or non-protein substance. **Claim 27** further limits the mutagenized amino acids of claim 1 to be in regions accessible to a binding partner. **Claim 28** further limits the mutagenized amino acids of claim 1 to be in a beta-sheet structure of a subunit of the protein.

Beste et al. teach an engineered protein derived from a beta-sheet structured protein (lipocalin) with a new antigen binding specificity. The beta-structured protein taught by Beste (page 1899, figure 1) anticipates the protein of claims 1 and 2. Beste also teach a set of criteria for selecting amino acids to be mutagenized (page 1900, right col. – 1901, left col. and page 1899, figure 1), and anticipates the various possible combinations of amino acids to be mutagenized, as recited in claims 3-6, 10, 11, 13, 27 and 28. The composition of claim 16 is also anticipated by the solution of ELISA binding assay as taught by Beste (page 1900, left col.).

Claim Rejections – 35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13, 16, 26-28 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chirgadze et al. (Acta Cryst. 1996. D52. 712-721) in view of Beste et al. (PNAS, March 1999, v96, p1898-1903).

Claim 7 is directed to a vertebrate crystallin protein mutagenized according to claim 1. **Claim 8** further limits the protein of claim 1 to be a gamma-crystallin protein. **Claim 9** further limits the protein of claim 1 to be a gamma-II-crystallin. **Claim 12** is directed to a bovine gamma-II-crystallin protein wherein at least one of Lys2, Thr4, Tyr6, Cys15, Glu17, Ser19, Arg36, and Asp38 is mutagenized. **Claim 26** further limits the protein of claim 7 to a bovine protein. **Claim 42** is directed to a mutagenized gamma crystalline polypeptide wherein the mutagenesis is selected from the group consisting of an insertion, a deletion, a substitution, and combinations thereof, such that the gamma crystalline polypeptide has a new binding property.

Chirgadze et al. teach a crystal structure of bovine gamma-II-crystallin which has a Greek-key beta-sheet motif (Chirgadze, page 717, figure 4) with amino acids exposed on the surface. Chirgadze also teach that the mutation of H15C affects surface hydrophobicity/hydrophilicity (Chirgadze, page 718, left col., 4th paragraph) and there are surface exposed cluster of residues including Lys2, Glu17, Arg36 and Asp38 (Chirgadze, page 718, right col., 4th paragraph).

Chirgadze et al. do not teach mutagenizing the surface exposed residues to arrive at new antigen-binding activity.

Beste et al. teach the engineering of a beta-sheet structured protein (lipocalin), by mutagenizing selected amino acid residues, resulting in new antigen-binding activity,

as set forth above. Beste et al. also teach the general criteria for selecting amino acids to mutagenize (page 1900, right col. – 1901, left col.)

It would have been obvious to one of ordinary skill in the art at the time of the invention to mutagenize any of the residues Lys2, Glu17, Arg36 and Asp38 forming a highly charged cluster of surface residues on the beta-sheet structure of bovine gamma-II-crystallin protein as taught by Chirgadze (Chirgadze, page 718, right col. 4th paragraph) using the engineering principle and criteria as taught by Beste where the motivation would have been to apply the design principles to the crystallin structure of Chirgadze as an alternate protein scaffold for the design of novel binding site (Beste, page 1903, left col, 3rd paragraph).

Claims 1-6, 10, 11, 13-16, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saviranta et al. (IDS: Protein Engineering, 1998, 11:143-152) in view of Beste et al. (PNAS, March 1999, v96, p1898-1903).

Claim 14 is directed to a beta-sheet structured protein according to claim 1 that has binding specificity for a compound selected from estradiol and BSA-b-estradiol-17-hemisuccinate. Claim 15 is directed to a protein according to claim 1 but also has binding specificity for estradiol or BSA-estradiol-17-hemisuccinate, wherein the protein comprises SEQ ID NO:21 (bovine gamma-crystalline, see attached STIC search result).

Saviranta et al. teach engineering using random mutagenesis of an antibody to gain binding specificity towards estradiol and other derivatives.

Saviranta et al. do not teach engineering of a beta-sheet structured protein to have binding specificity toward estradiol.

Beste teach the engineering of a beta-sheet structured protein to gain new ligand binding specificities toward well-know immunological hapten (Beste, page 1901, left col. 3rd paragraph) and the potential of small molecule scaffolds to replace antibody as antigen binding molecules (Beste, page 1903, right col. last sentence).

It would have been obvious to one of ordinary skill in the art at the time of the invention to apply the beta-sheet structured protein engineering protocol as taught by Beste to redesign a beta-sheet structured protein to bind to estradiol, similar to the protein engineering of antibody taught by Saviranta, where the motivation would have been to replace the bulkier antibody molecule with smaller beta-sheet structured protein scaffolds as taught by Beste (Beste, page 1989, abstract, last sentence).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew C Lee whose telephone number is (571) 272-2931. The examiner can normally be reached on 9am - 5pm, Mon - Fri..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Matthew C Lee, Ph.D.
Examiner
Art Unit 1631

MARJORIE MORAN
PATENT EXAMINER

2/1/05

Marjorie A. Moran
2/9/05